14

TENT COOPERATION TREATY

REC'D 11 MAY 2001

WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
FP68812/RMK		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/04349	18/02/2000	22/02/1999
International Patent Classification (IPC) or national classification and IPC		
C12Q1/00		
Applicant		
LYNX THERAPEUTICS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21/08/2000	09.05.2001
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Bradbrook, D Telephone No. +49 89 2399 7413

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/04349

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-67 as originally filed

Claims, No.:

1-18 as originally filed

Drawings, sheets:

1/19-19/19 as originally filed

Sequence listing part of the description, pages:

1-8, filed with the letter of 23.05.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
   see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,4,16-18
	No:	Claims	1,3,5-15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations
   see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the

claims are fully supported by the description, are made:
see separate sheet

Section I

1. Sequence listing pages 1-8, filed with the letter of 23.05.00, are included in the basis of this written opinion. Said sequence listing pages do not form part of the application (Rule 13ter.1(f) PCT).

Section V

2. Reference is made to the following documents:

   D1: WO 95-A-25538 (Gen.Hosp.Corp; Leland Stanford Junior Univ.; 28.09.95);
   D2: WO 98-A-12352 (Gen.Hosp.Corp; Leland Stanford Junior Univ.; 26.02.98);
   D3: EP-A-0 735 144 (Japan Res.Dev.Corp.; 02.10.96);
   D4: WO 98-A-40515 (Samadpour; 17.09.98);
   D5: WO 96-A-12014 (Lynx Therapeutics Inc; 25.04.96);
   D6: WO 96-A-41011 A (Spectragen Inc 19.12.96) cited in the application;
   D7: WO 96-A-12039 A (Lynx Therapeutics Inc 25.04.96) cited in the application.

3. Novelty and Inventive step

a. Documents D1 and D2 show methods for cloning polymorphic restriction fragments. The fragments are generated by cleavage with a first restriction enzyme; those fragments containing a polymorphic site specific for a second restriction enzyme are enriched (see Example XI and Fig.9, which are the same in D1 and D2). The cloning of a plurality of such fragments, as indicated in the Example cited, provides a library of fragments. As such, D1 and D2 appear to prejudice the novelty (Article 33(2) PCT) of present claims 1, 13, and 14. Moreover, cloning requires that the fragments are contained in a replicable vector, so that claim 3 is also not novel.

b. It should be noted that the subject-matter of claims 13 and 14 is not novel per se: any library of restriction fragments taken from a plurality of individuals will by chance contain restriction site polymorphisms with respect to a second endonuclease.

c. Dependent claims 2 and 4 differ from D1 and D2 in that the fragments comprise oligonucleotide tags. Such tags are well-known in the art for indexing and sorting nucleic acid molecules (e.g. D5-D7, especially D6 claim 69), and it is not considered to require inventive activity on the part of the skilled person to use such tags in the methods of D1 and D2 for keeping track of the fragments generated. Therefore, said claims 2 and 4 appear not to be inventive (Article 33(3) PCT).

d. The scope of claim 5 would appear to include a composition comprising microparticles having attached thereto any two or more different sequence-specific probes. Such subject-matter is not novel (Article 33(2) PCT): oligonucleotide probes attached to microparticles are often used for capture of target oligonucleotides, such as in D7 (p.18, l.29ff). The same applies to claim 9, in which the probes are in an array on a solid support (cf D7: claims 19-22). Similarly, dependent claims 6-8 and 10-12, in which each subpopulation comprises an oligonucleotide tag, are not novel (see D5-D7).

e. The method of claim 15 does not appear to contain any technical features that distinguish it from the method outlined in Fig.9 and Example XI of D1 and D2. Thus, claim 15 appears to be not novel (Article 33(2) PCT). Dependent claim 16 appears not to be inventive (Article 33(3) PCT), as the removal of repetitive sequences is a standard step, particularly when using genomic DNA.

f. Claim 17 is directed to a method in which two pools of nucleic acid are restricted with one enzyme, enriched for fragments containing a polymorphism with respect to a second restriction enzyme, then probed for the polymorphic site to determine the ratio of polymorphism between the two pools. This seems not to be inventive: a standard analysis of different populations of nucleic acid may include enzymatic restriction, resolution on an electrophoretic gel (each resolved band may be considered as an enriched population), and contact with known labelled probes to quantify the presence of a particular polymorphism, which may be at a restriction site. Thus, claim 17 is not inventive in the sense of Article 33(3) PCT. Such an analysis is often applied to nucleic acid from cells or tissues displaying different phenotypes, so that claim 18 is also not inventive.

g. Neither of documents D3 and D4 is considered prejudicial to the present claims. Both documents disclose methods in which pools of DNA molecules are sequentially restricted using two different enzymes. However, D4 uses this to provide a distinctive fragmentation pattern seen after electrophoretic separation (Example 3; claim 16); in D3 this is a tool to allow classification of DNA, and does not involve enrichment of subregions polymorphic for one of the enzymes as in present claim 1 (D3: Figs 1, 3 and claims).

Section VI

4. Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO-A-99 23256	14.05.99	30.10.98	30.10.97*

*priority not checked

The priority for the present application is deemed to be valid. Therefore, the above document is not considered to be part of the prior art for the purposes of Article 33(2) and (3) PCT. However, should the present application enter the national or regional phase, the above document could be relevant to the question of novelty.

Section VII

5. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.

6. The citation of non-published patent documents which have not been made available to the public (e.g. on pages 37 and 38), rather than their equivalent publication numbers, means that the application is not self-contained (PCT Guidelines C-II, 4.18).

Section VIII

7. The following objections are under Article 6 PCT:

a. The term "polymorphic consensus sequence", used in claims 1, 5 and 9, is unclear and leaves the reader in doubt as to the exact nature of the subject-matter being claimed, thereby rendering the definition of the subject-matter of said claims unclear. Said claims also fail to define precisely the nature of the nucleic acid fragments and polymorphic probes in that they are said to "comprise" certain features: this means that the molecules include these features, but are not limited thereto.

b. In claim 3, it is unclear what relation the vector has to the nucleic acid fragments in the library, as it is not specified that the fragments are contained in the replicable vector.

c. Claim 15 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. With respect to formation of the two populations of single-stranded DNA fragments, the claim attempts to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result are lacking.

d. Claim 18 is unclear as it erroneously refers back to itself.